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Serum glucose, triglycerides and cholesterol in relation to prostate cancer death in the Swedish AMORIS study

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Abstract

Purpose: Lifestyle-related conditions such as obesity are associated with prostate cancer progression, but the link with hyperglycemia and dyslipidemia is unclear. This study, therefore, aims to explore how glucose, triglycerides and total cholesterol are associated with prostate cancer death.

Methods: From the Swedish AMORIS cohort, we selected 14150 men diagnosed with prostate cancer between 1996 and 2011 who had prediagnostic measurements of serum glucose, triglycerides and total cholesterol. Multivariable Cox proportional hazards models were used to determine the hazard ratios for death in relation to the aforementioned metabolic markers adjusting for potential confounders.

Results: Using clinical cut-off points, a non-significant positive association was observed between glucose and prostate cancer death. When compared to those with glucose in the lowest quartile, those in the highest quartile had greater risk of prostate cancer death (HR: 1.19; 95% CI: 1.02-1.39). However, neither total cholesterol nor triglycerides were associated with prostate cancer death. Glucose and triglycerides were positively associated with overall, cardiovascular and other deaths. Hypercholesterolemia was only associated with risk of CVD death.

Conclusion: Our results suggest that glucose levels may influence prostate cancer survival, but further studies using repeated measurements are needed to further elucidate how glucose levels may affect prostate cancer progression.

Introduction

Prostate cancer is a leading cause of deaths among men globally (1), which, according to epidemiological studies, may be partly due to lifestyle-related factors (2,3). For instance, a recent study demonstrated that incidence of lethal prostate cancer was higher among men with poorer lifestyle habits characterised by high intake of energy-dense foods, high alcohol intake, physical inactivity and smoking (4). In line with this, several epidemiological studies reported that life-style related conditions such as metabolic syndrome and obesity were associated with increased risk of prostate cancer death (2,5,6). Other metabolic disorders including hyperglycemia and dyslipidemia have also been associated with lower survival for other types of cancers such as breast, colorectal and pancreatic cancer, but research on their associations with prostate cancer death is sparse and inconclusive (2,7-10).

Moreover, experimental evidence purports that glucose and lipid aberrations trigger prostate cancer progression by inducing carcinogenic processes such as cell proliferation and growth, inflammation, and DNA damage. One study reported that hyperinsulinemia, a phenotype of diabetes, increases levels of circulating free bioactive insulin growth factor (IGF-1) by inhibiting the secretion of IGF binding protein-1 (IGFBP-1) and SHBG resulting in tumor cell growth, proliferation and migration (11,12). Similarly, dyslipidemia has been implicated with altering signalling pathways, including PTEN and PI3K/AKT, which control cell proliferation, and migration (13).

To provide greater insight into the role that metabolic disturbances may play in relation to prostate cancer progression, in this study, we investigated the associations between pre-diagnostic serum glucose, triglycerides and cholesterol and prostate cancer death among men with prostate cancer. We also conducted stratified analyses by prostate cancer risk category and competing risk analyses to assess the potential effects of competing events on our findings.

Materials and Methods

Study design and population

A detailed description of the Swedish Apolipoprotein MOrtality RISk (AMORIS) cohort has been published elsewhere (14,15). Briefly, the database included 812,073 Swedish men and women with blood samples which were assessed at the Central Automation Laboratory (CALAB) in Stockholm, Sweden, during the period 1985 to 1996 (16-18). Individuals enrolled in the study were primarily from the greater Stockholm area and, were either healthy and having laboratory testing as part of a general health check or outpatients referred for laboratory testing. None of the participants were inpatients at the time of sampling. The CALAB data was linked to several Swedish national registries including the Swedish National Cancer Register, the Hospital Discharge Register, the Cause of Death Register, the consecutive Swedish Censuses during 1970-1990, and the National Register of Emigration using the Swedish 10-digit personal identity number (REF).

For the present analysis, the AMORIS cohort was linked to the National Prostate Cancer Register (NPCR), which has been nationwide since 1998 (19). This Register, which includes 98% of all newly diagnosed prostate cancer cases registered in the Swedish National Cancer Register to which reporting is mandated, aims to provide data for quality assurance (19) . We retrieved information on date of diagnosis, age at diagnosis, pathological TNM stage, Gleason score and serum concentration of PSA at time of diagnosis from the NPCR (16). We utilise information on TNM stage, Gleason score, and serum concentration of PSA at time of diagnosis to generate the prostate cancer risk category which was defined in accordance with an adapted version of National Comprehensive Cancer Network as low risk (T1-2, Gleason score 2–6 and PSA <10 ng/ml), intermediate risk (T1-2, Gleason score 7 and/or PSA 10 to <20 ng/ml), high risk (T3 and/or Gleason score 8–10 and/or PSA 20 to <50 ng/ml), and regionally metastatic tumors (T4 and/or N1 and/or PSA 50 to <100 ng/ml in the absence of distant metastases (M0 or MX)) and distant metastatic tumors (M1 and/or PSA >100 ng/ml) (19). Information on educational level was abstracted from the Population and Housing Census for 1970-1990 while information on the participants' comorbidity status was abstracted from the National Patient Register. Using information on the participants' status, we calculated the Charlson Comorbidity Index which includes 19 diseases, with each disease category assigned a weight. We then totalled the weights to create a score which was categorised into four levels (0, 1, 2, and ≥3), and ranged from no co-morbidity to severe co-morbidity (20).

Men were excluded from this study if they did not have any information on PSA levels, Gleason grade, and TNM stage (n= 5995) or if their glucose, total cholesterol and triglycerides measurements were not taken at the same health examination (n= 2991). After exclusion, our study comprised 14,150 men aged 20 and older with a primary prostate cancer diagnosis between 1996 and 2011 (Figure I).

Pre-diagnostic serum levels of glucose, triglycerides and total cholesterol were our main exposures. For the purpose this study we selected the most recent serum measurement which was taken approximately 14 years prior to diagnosis. Serum levels of glucose, total cholesterol and triglycerides were determined enzymatically (21) using fully automated systems with automatic calibration (17). All analyses were done at an accredited laboratory (17).

For our analyses, serum glucose, total cholesterol and triglycerides levels were classified based on clinical cut-off points from the American Diabetes Association and National Cholesterol Education Programme (NCEP) guidelines (22-24), and as quartiles. For the clinical cut-off points, serum glucose levels were categorised as <5.6mmol/l, 5.6-6.9mmol/l and >6.9mmol/l, while serum total cholesterol was classified as <5.18mmol/l, 5.18mmol/l-6.19mmol/l, and >6.19mmol/l and serum triglycerides as <1.7mmol/l, 1.7-2.24mmol/l, and >2.24mmol/l. The lowest clinical cut-off points and quartiles were selected as the reference category.

The outcome of interest was prostate cancer death. To assess the role of competing risks, we also included overall, cardiovascular (CVD) and other deaths as outcomes. Prostate cancer death was defined using ICD-10 code C61. Cardiovascular death was defined using ICD-10 codes I0-I78, while death from other causes included all deaths except prostate cancer and CVD deaths.

The study complied with the Declaration of Helsinki and was approved by the Ethics Review Board of the Karolinska Institute.

Statistical analysis

Cox proportional hazards regression was conducted to calculate the hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between serum glucose, total cholesterol and triglycerides and deaths (overall, prostate cancer, CVD and other) with age as the underlying timescale. Participants were followed from age at diagnosis of primary prostate cancer to age at death from any cause, emigration or end of study (December 31st, 2011), whichever came first.

In multivariable analyses, our main models were adjusted for age at diagnosis (as a quadratic function), educational level (low- (primary school or less), intermediate (high school), high-(higher education)), CCI (0, 1, 2, ≥3), fasting status (fasting, non-fasting), and mutually adjusted for serum glucose (continuous), total cholesterol (continuous) and triglycerides (continuous) (model 1). For prostate cancer death, we additionally adjusted for prostate cancer risk category (low risk, intermediate risk, high risk, regional metastatic, distant metastatic, missing) in separate analyses. We also conducted stratified analyses by prostate cancer risk category to assess the differences in the association between the serum markers and prostate cancer death within strata of the prostate cancer risk category. Tests for interaction between the markers and prostate cancer risk category were assessed using the Wald test.

We used Schoenfeld residuals to test the proportional hazards assumption; there was no evidence to suggest that the assumption was violated.

To evaluate the shape of the relation between the continuous exposures (glucose, triglycerides and total cholesterol) and prostate cancer death, glucose, triglycerides and total cholesterol were modelled by two-tailed restricted cubic splines with four knots of the distribution in a Cox proportional hazards regression model (25).

Hyperglycemia and dyslipidemia are strongly associated with overall mortality (26,27). Hence, we used the Fine and Gray competing-risks regression to account for the potential effect of competing risks on our findings, whereby CVD deaths and other deaths were considered as competing events (28). As inclusion of men with non-fasting serum measurements may affect the estimates, we also conducted a sensitivity analysis including only men with fasting measurements to evaluate the association between the metabolic markers

and death. In order to examine whether latent cancer might have affected the exposure measurements, we excluded the first 2 years of follow-up from our analyses. Body mass index (BMI) is associated with both the exposure measurements and prostate cancer death and may be an important confounder in our study. However, BMI could not be included as a covariate in our multivariable analyses due to the high proportion of missing information on BMI (78.5%). In subgroup analyses among men with information on BMI (n=3,073), which was taken at the same time with blood draw (i.e. least 14 years prior to diagnosis), we adjusted for BMI to assess its effect on the association between the metabolic markers and death. Missing values were considered as a separate category in the statistical models.

Data management was conducted with Statistical Analysis Software (SAS) release 9.4 (SAS Institute, Cary, NC), while statistical analyses were conducted with Stata release 13.1 and 14.1 (StataCorp, College Station, TX, USA).

Results

Mean age at prostate cancer diagnosis in the study population was 68 (standard deviation (SD) = 8.0) years (**Table 1)**. Approximately 1/3 of men were diagnosed with low risk prostate cancer. Among the 3,223 men who died during a mean follow-up time of approximately 4 years, 1,473 died from prostate cancer. Most men had at least a high school education . Mean serum concentrations for glucose, triglycerides and total cholesterol were 5.1mmol/l, 1.5mmol/l and 5.9mmol/l, respectively. Generally, the study characteristics for those who were excluded from the study were similar to those who were included in the study (Table S1).

Glucose

After adjusting for age, educational level, CCI, fasting status, triglycerides and total cholesterol, we observed that men with glucose levels in the pre-diabetic and diabetic range had increased risk of prostate cancer death (HR: 1.15; 95% CI: 1.00-1.32 and 1.29; 1.00-1.67 for glucose levels of 5.6-6.9mmol/L and >6.9mmol/L respectively; p for trend: 0.01) (**Table 2)**. The statistically significant trend disappeared after additional adjustment for prostate cancer risk category. When considering quartiles of glucose level, men with glucose in the highest quartile had a higher risk of prostate cancer death than those in lower quartile (HR: 1.27; 95% CI: 1.09-1.48; p for trend: <0.01). The association was further attenuated after additional adjustments for

prostate cancer risk category but remained statistically significant (HR: 1.19; 95% CI: 1.02-1.39; p for trend: 0.04). The association between glucose and prostate cancer death, however, did not differ by prostate cancer risk categories (p for interaction: 0.21) **(Table 4)**. Glucose was also positively associated with overall death, and other deaths based on both the clinical cut-off points and quartiles **(Table 2)**. Men with high glucose levels (>6.9mmol/L) defined by clinical cut-off points also had an increased risk of CVD death.

In a restricted cubic spline model, our finding demonstrated no evidence of a non- linear association between glucose and prostate cancer death (p for non-linearity=0.83) **(Figure 2)**.

Triglycerides

When considering the clinical cut-off points and quartile distribution, triglycerides was not associated with prostate cancer death in multivariable analyses (**Table 2)**. In analyses stratified by prostate cancer risk category, similar null findings for the association between triglycerides and risk of prostate cancer death was seen (p for interaction: 0.37) **(Table 4)**. Triglycerides, however, was positively associated with overall, CVD and other deaths irrespective of the cut-off points used **(Table 2)**. There was no evidence a non-linear association between triglycerides and prostate cancer death (p for non-linearity= 0.33) **(Figure 2)**.

Total cholesterol

Total cholesterol was not associated with prostate cancer death overall, or when stratified by prostate cancer risk category (p for interaction: 0.21) (**Tables 2 and 4)**. There was also no association between total cholesterol and overall and other deaths. However, based on clinical cut-off points, hypercholesterolemic men (>6.19 mmol/L) had higher risk of CVD death than those with normal cholesterol levels (<5.18mmol/L). Similar positive associations were seen for quartiles of total cholesterol.

There was no evidence of a non-linear association between total cholesterol and prostate cancer survival (p for non-linearity 0.36) **(Figure 2)**.

Sensitivity analyses

After excluding men with non-fasting measurements, the directions of the associations between metabolic markers and prostate cancer death virtually remained the same **(Tables S2)**. Similarly, in analyses where we excluded the first 2 years of follow-up, the directions of the associations remained unchanged. In competing risk analyses, the estimates using Fine and Gray competing risk regression and Cox proportional hazards models were not materially different **(Table S3)**. Finally, in analyses involving a subgroup of men with information on BMI, the directions of the associations did not vary substantially following inclusion of BMI as a covariate in the fully adjusted model **(Table S4)**.

Discussion

In this large prospective study, we observed a weak positive association between serum levels of glucose and prostate cancer death, but no associations were observed for triglycerides and total cholesterol. Glucose and triglycerides were positively associated with overall, CVD or other deaths. Hypercholesterolemia was also positively associated with CVD death.

Glucose

Consistent with other studies we found positive associations between glucose and prostate cancer death (10,29). Other studies yielded non-significant associations between diabetes and prostate cancer death, but the associations were positive in most of these studies (30-32). Although, previous epidemiological studies provide evidence suggesting that the severity of the disease may modify the effect of risk factors which potentially influence prostate cancer progression on prostate cancer survival (5,33), in the current study, we did not observe any modifying effect of the severity of the disease on the association between glucose and prostate cancer death.

Obesity, which is associated with glucose aberrations and prostate cancer death (5,6,12), may also partly explain the observed positive association between glucose and prostate cancer death, but the inclusion of BMI in our multivariate models had virtually no effect - suggesting that BMI is not an important confounder in our study.

In line with our findings, metformin, an antidiabetic drug, has been shown to improve prostate cancer survival (34). Other studies using in vivo and in vitro models also demonstrated that glucose metabolism contributes to prostate cancer progression by inducing tumor cell proliferation, survival and migration (35,36). For instance, one study found that a diet high in refined carbohydrates promoted tumor growth by increasing IGF-1 levels and activating Akt signalling pathway in mice (36).

Triglycerides

To date, very few studies have investigated the association between triglycerides and prostate cancer death. Similar to our study, two small studies found non-significant positive associations between triglycerides and prostate cancer death (37,38). In contrast, another study reported a non-significant inverse association between triglycerides and prostate cancer-specific death (32).

Despite the lack of association between triglycerides and prostate cancer in the present study, experimental studies suggest that triglycerides may induce prostate cancer progression. For instance, several studies have shown that triglyceride-rich remnant like particles induced PC-3 cell proliferation by upregulating pathways such as MEK/ERK and/or Akt pathways, which are responsible for regulating cancer-associated processes including cell growth and proliferation, and cell cycle arrest (39,40).

Total cholesterol

Similar to the HUNT 2 study, we did not find any association between total cholesterol and prostate cancer death in the overall study population (32). Interestingly, though, the findings based on quartiles of total cholesterol and our spline model suggested a non-significant inverse association between total cholesterol and prostate cancer death. Haggstrom et al. also reported an inverse, but non-significant, association between total cholesterol and prostate cancer death (8). This finding may be due to the influence of latent cancer. However, in analyses where we excluded the first two years of follow-up, the tendency remained.

Although epidemiological studies, so far, do not support an association between total cholesterol and prostate cancer survival, an association between total cholesterol and prostate cancer survival cannot be negated as evidence from experimental studies has associated this exposure with mechanisms which are known to

induce progression of cancer. Intervention studies, for example, showed that statins inhibit prostate cancer development and progression by suppressing the enzyme HMG-CoA reductase and hence *de novo* steroidogenesis (41,42). Further, one recent study showed that cholesterol increased activity of TRMP7 resulting in activation of AKT and/or the ERK pathway and increased proliferation of prostate cells (43). Other studies indicated that a hypercholesterolemic diet induced prostate cancer development and progression in mice (44,45).

Competing risk

Prostate cancer is a disease which primarily affects the older men (46) who are also at greater risk of developing metabolic-related comorbidities such as cardiovascular diseases that may alter a man's probability of dying from the cancer itself (47,48). In this regard, several studies, including the present study, have implicated abnormal glucose, triglycerides, and total cholesterol levels with increased risk of overall, CVD and/or other deaths (10,27,49). Such competing events can contribute to underestimation of the associations between metabolic markers and prostate cancer death. However, the findings from our competing risk analyses imply that the presence of these events had virtually no effect on the association between the metabolic markers and prostate cancer death in the present study.

Strengths and limitations

One of the main strengths of this study is its relatively large sample size. Furthermore, our study population was selected from a population-based prostate cancer register with very high completeness. Furthermore, all exposure measurements were taken prior to diagnosis at the same laboratory; thereby allowing us to assess associations between the exposures and outcomes temporally. This study, however, has several limitations. A limitation of this study is the lack of repeated measurements for the metabolic markers which are known to have high intra-person variability. It is therefore likely that our study did not detect the true association between the exposures and the outcomes since we were unable to assess the cumulative effect that changes in the exposures over time, due to factors such as lifestyle changes and medication use, may have on the outcome. Although, the relatively long-time window between measurement of the exposure and date of diagnosis was another limitation of the present study, prostate cancer is a slow-growing disease which, according to autopsy studies, can be initiated as early as 20s and 30s in many men (50). Hence, our study

may reflect the fact that metabolic factors in the early progression phase may influence the natural history of the disease, and should be further investigated in future studies using repeated measures. It is also probable that misclassification of the exposures may have occurred as the participants' medication history (i.e. history of use of metformin and/or statin) or diabetic status was unknown, but the misclassification will most likely be non-differential. Finally, we did not have information on lifestyle-related behaviours such as smoking status and dietary history, but neither smoking nor diet is an established risk factor for prostate cancer death.

Conclusion

Our findings support a positive but weak association between glucose and prostate cancer death. Our study also confirmed that this exposure, as well as triglycerides and total cholesterol, are important predictors of overall deaths and/or CVD deaths. Taken together, our findings provide support for the hypothesis that improved metabolic control by means of lifestyle changes or pharmacological treatment may contribute to improving survival in men with prostate cancer. However, further epidemiological studies, using repeated measurements to better account for the cumulative effect of the exposures on the outcomes, combined with experimental studies are warranted to substantiate our findings.

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Results

Table 1: Characteristics of the study population, Swedish AMORIS cohort

Characteristics	**Total cohort (N= 14,150)**
Age at diagnosis (years)	
Mean (SD)	68 (8.0)
N (%)	
≤49	93 (0.7)
50-59	1953 (13.8)
60-69	6267 (44.3)
≥ 70	5837 (41.3)
CCI	
0	10776 (76.2)
1	1755 (12.4)
2	1056 (7.5)
3+	453 (3.2)
Missing	110 (0.8)
Education	
N (%)	
High	4396 (31.1)
Intermediate	5843 (41.3)
Low	3698 (26.1)
Missing	213 (1.5)
Follow-up time	
Mean (SD)	4.0 (3.0)
Interval time between measurement taken on entry and prostate cancer diagnosis (years)	
Mean (SD)	14 (4.5)
Glucose (mmol/L)	
Mean (SD)	5.2 (1.2)
N (%)	
<5.60	11155 (78.8)
5.6-6.9	2455 (17.4)
>6.9	540 (3.8)
Triglycerides (mmol/L)	
Mean (SD)	1.6 (1.2)
N (%)	
<1.70	9460 (66.9)
1.70-2.24	2384 (16.9)
≥2.25	2306 (16.3)
Total cholesterol (mmol/L)	
Mean (SD)	5.9 (1.0)
N (%)	
<5.18	3293 (23.3)
5.18-6.19	5378 (38.0)
>6.19	5479 (38.7)
Fasting status	
N (%)	
Fasting	8485 (60.0)
Non-fasting	5665 (40.0)
Prostate cancer risk categories	
N (%)	
Low risk	4432 (31.3)
Intermediate risk	3988 (28.2)
High risk	3226 (22.8)
Regional/distant metastatic	2160 (15.3)
Missing	344 (2.4)

Vital statistics	
N (%)	
Alive	10927 (77.2)
All deaths	3223 (22.8)
Prostate cancer deaths	1473 (10.4)
CVD deaths	722 (5.1)
Other deaths	1028 (7.3)

- **Abbreviations**: N= number, CCI= Charlson comorbidity index, CVD= cardiovascular disease

Table 2: Adjusted hazard ratios (HRs) and 95% CI for the association of serum glucose, triglycerides and total cholesterol levels with risk of overall, and cause-specific death among men with newly diagnosed prostate cancer, Swedish AMORIS cohort**,** (N=14150)

		Overall death		Prostate cancer death			CVD death		Other death	
	Person-years	**No. of deaths**	**HR (95% CI)**	**No. of deaths**	**HR (95% CI)**	**HR (95% CI)***	**No. of deaths**	**HR (95% CI)**	**No. of deaths**	**HR (95% CI)**
Glucose (mmol/L)										
<5.60	**60355**	**2370**	1.00 (Ref)	**1106**	1.00 (Ref)	1.00 (Ref)	**553**	1.00 (Ref)	**731**	1.00 (Ref)
5.6-6.9	**10652**	**656**	1.16 (1.05-1.27)	**291**	1.15 (1.00-1.32)	1.08 (0.94-1.24)	**142**	1.06 (0.87-1.29)	**223**	1.24 (1.06-1.46)
>6.9	**2303**	**197**	1.45 (1.24-1.71)	**76**	1.29 (1.00-1.67)	1.10 (0.85-1.43)	**47**	1.47 (1.06-2.04)	**74**	1.66 (1.27-2.18)
P for trend			**<0.01**		**0.01**	**0.22**		**0.05**		**<0.01**
Quartiles (mmol/L)										
≤4.5	**17200**	**596**	1.00 (Ref)	**266**	1.00 (Ref)	1.00 (Ref)	**150**	1.00 (Ref)	**180**	1.00 (Ref)
4.6-4.8	**14983**	**798**	1.02 (0.91-1.14)	**380**	1.12 (0.95-1.32)	1.10 (0.93-1.30)	**169**	0.85 (0.68-1.09)	**249**	1.00 (0.81-1.22)
4.9-5.4	**22563**	**853**	1.02 (0.92-1.13)	**396**	1.13 (0.97-1.32)	1.08 (0.93-1.26)	**188**	0.89 (0.72-1.09)	**269**	0.98 (0.82-1.18)
≥5.5	**18564**	**976**	1.19 (1.08-1.32)	**431**	1.27 (1.09-1.48)	1.19 (1.02-1.39)	**215**	0.95 (0.77-1.17)	**330**	1.28 (1.07-1.53)
P for trend			**<0.01**		**<0.01**	**0.04**		**0.76**		**0.01**
Triglycerides (mmol/L)										
<1.70	**50150**	**2104**	1.00 (Ref)	**980**	1.00 (Ref)	1.00 (Ref)	**461**	1.00 (Ref)	**663**	1.00 (Ref)
1.70-2.24	**11624**	**556**	1.01 (0.92-1.12)	**233**	0.94 (0.81-1.09)	0.93 (0.80-1.08)	**128**	1.18 (0.96-1.44)	**195**	1.03 (0.86-1.23)
≥2.25	**11535**	**563**	1.12 (1.01-1.24)	**260**	1.06 (0.91-1.23)	1.02 (0.88-1.18)	**133**	1.24 (1.00-1.53)	**170**	1.13 (0.94-1.35)
P for trend			**0.04**		**0.65**	**0.96**		**0.03**		**0.21**
Quartiles (mmol/L)										
≤0.8	**17590**	**620**	1.00 (Ref)	**301**	1.00 (Ref)	1.00 (Ref)	**137**	1.00 (Ref)	**182**	1.00 (Ref)
0.9-1.2	**14757**	**829**	1.13 (1.01-1.26)	**369**	1.11 (0.94-1.30)	1.02 (0.87-1.20)	**182**	1.12 (0.88-1.43)	**278**	1.21 (1.00-1.47)
1.3-1.8	**20416**	**891**	1.18 (1.06-1.30)	**403**	1.16 (1.00-1.34)	1.09 (0.94-1.26)	**200**	1.32 (1.06-1.64)	**288**	1.13 (0.94-1.36)
≥1.9	**20547**	**883**	1.22 (1.10-1.36)	**400**	1.14 (0.97-1.34)	1.08 (0.92-1.26)	**203**	1.38 (1.10-1.74)	**280**	1.88 (1.06-1.55)
P for trend			**<0.01**		**0.09**	**0.27**		**<0.01**		**<0.01**
Total cholesterol (mmol/L)										
<5.18	**17469**	**699**	1.00 (Ref)	**323**	1.00 (Ref)	1.00 (Ref)	**135**	1.00 (Ref)	**241**	1.00 (Ref)
5.18-6.19	**28109**	**1238**	0.99 (0.90-1.08)	**561**	0.97 (0.84-1.11)	0.94 (0.82-1.08)	**279**	1.17 (0.95-1.45)	**388**	0.91 (0.77-1.08)
>6.19	**27731**	**1286**	1.01 (0.92-1.12)	**589**	1.01 (0.88-1.16)	1.00 (0.87-1.15)	**308**	1.30 (1.05-1.60)	**399**	0.86 (0.73-1.01)
P for trend			**0.74**		**0.80**	**0.90**		**0.01**		**0.08**
Quartiles (mmol/L)										
≤5.10	**17469**	**699**	1.00 (Ref)	**323**	1.00 (Ref)	1.00 (Ref)	**135**	1.00 (Ref)	**241**	1.00 (Ref)
5.2-5.8	**16810**	**860**	0.98 (0.88-1.09)	**387**	0.96(0.82-1.13)	0.93 (0.80-1.09)	**198**	1.21 (0.96-1.54)	**275**	0.87 (0.73-1.05)
5.9-6.5	**18553**	**837**	1.01 (0.91-1.12)	**399**	1.02 (0.88-1.18)	1.03 (0.89-1.19)	**189**	1.19 (0.95-1.50)	**249**	0.90 (0.75-1.07)
≥6.60	**20478**	**827**	1.00 (0.91-1.11)	**364**	0.97 (0.84-1.13)	0.94 (0.81-1.09)	**200**	1.29 (1.03-1.61)	**263**	0.89 (0.74-1.06)
P for trend			**0.81**		**0.92**	**0.69**		**0.04**		**0.25**

- **Abbreviations:** CVD= cardiovascular disease
- All models were adjusted for educational level, CCI, fasting status and mutually adjusted for glucose, triglycerides, and total cholesterol
- * Adjusted for the abovementioned covariates plus prostate cancer risk category

Table 3: Adjusted sub-hazard ratio (SHR) and 95% CI for the associations between serum glucose, triglycerides and total cholesterol levels and risk of prostate cancer death among men with newly diagnosed prostate cancer, Swedish AMORIS cohort (N=14150)

	Adjusted SHR (95% CI)
Glucose (mmol/L)	
<5.6	1.00 (Ref)
5.6-6.9	1.14(0.99-1.31)
>6.9	1.18 (0.90-1.54)
P for trend	**0.04**
Quartiles (mmol/L)	
≤4.5	1.00 (Ref)
4.6-4.8	1.13 (0.93-1.33)
4.9-5.4	1.14 (0.98-1.32)
≥5.5	1.26 (1.08-1.46)
P for trend	**<0.01**
Triglycerides (mmol/L)	
<1.70	1.00 (Ref)
1.70-2.24	0.91 (0.78-1.06)
≥2.25	1.02 (0.88-1.19)
P for trend	**0.96**
Quartiles (mmol/L)	
≤0.8	1.00 (Ref)
0.9-1.2	1.04 (0.88-1.22)
1.3-1.8	1.11 (0.96-1.29)
≥1.90	1.07 (0.91-1.25)
P for trend	**0.32**
Total cholesterol (mmol/L)	
<5.18	1.00 (Ref)
5.18-6.19	0.97 (0.84-1.11)
>6.19	1.01 (0.87-1.16)
P for trend	**0.85**
Quartiles (mmol/L)	
≤5.1	1.00 (Ref)
5.2-5.8	0.95 (0.82-1.12)
5.9-6.5	1.03 (0.89-1.20)
≥6.6	0.96 (0.83-1.12)
P for trend	**0.88**

- Models were adjusted for educational level, CCI, fasting status and mutually adjusted for glucose, triglycerides, and total cholesterol
- Abbreviation: SHR- sub-distribution hazard ratio

Table 4: Adjusted hazard ratios (HRs) and 95% CI for the associations between prostate cancer death and quartiles of serum glucose, triglycerides and total cholesterol by prostate cancer risk categories among men with newly diagnosed prostate cancer, Swedish AMORIS cohort (N=14150)

	No. of events	Low risk	No. of events	Intermediate risk	No. of events	High risk	No. of events	Regional/distant Metastatic	P for interaction
						HR (95%CI)			
Glucose (mmol/L)									
≤4.5	10	1.00 (ref)	29	1.00 (ref)	59	1.00 (ref)	169	1.00 (ref)	
4.6-4.8	19	3.43 (1.36-8.69)	37	1.17 (0.70-1.98)	99	1.07 (0.76-1.49)	227	1.09 (0.88-1.35)	0.21
4.9-5.4	10	1.53 (0.57-4.08)	29	1.04 (0.64-1.70)	93	1.15 (0.85-1.56)	261	1.02 (0.84-1.23)	
≥5.5	12	2.19 (0.84-5.71)	44	1.15 (0.70-1.89)	108	1.14 (0.83-1.54)	265	1.19 (0.98-1.46)	
P for trend		0.49		0.71		0.37		0.14	
Triglycerides (mmol/L)									
≤0.8	11	1.00 (ref)	29	1.00 (ref)	69	1.00 (ref)	191	1.00 (ref)	
0.9-1.2	11	2.13 (0.94-4.81)	39	1.03 (0.61-1.72)	92	1.25 (0.91-1.72)	230	0.92 (0.75-1.13)	0.37
1.3-1.8	14	1.57 (0.71-3.50)	46	1.07 (0.66-1.72)	93	1.03 (0.75-1.41)	249	1.09 (0.90-1.32)	
≥1.90	12	0.98 (0.38-2.53)	25	0.93 (0.56-1.56)	105	1.23 (0.89-1.68)	252	1.02 (0.83-1.24)	
P for trend		0.88		0.85		0.40		0.50	
Total cholesterol (mmol/L)									
≤5.1	13	1.00 (ref)	34	1.00 (ref)	82	1.00 (ref)	197	1.00 (ref)	
5.2-5.8	14	1.11 (0.51-2.40)	41	1.03 (0.62-1.71)	102	1.07 (0.78-1.47)	232	0.91 (0.74-1.11)	0.23
5.9-6.5	15	1.08 (0.50-2.33)	34	0.89 (0.54-1.46)	85	0.96 (0.70-1.31)	262	1.06 (0.88-1.28)	
≥6.6	9	0.63 (0.27-1.51)	30	1.11 (0.69-1.80)	90	1.05 (0.77-1.42)	231	0.87 (0.72-1.05)	
P for trend		0.32		0.79		0.94		0.33	

* All models were adjusted for educational level, CCI, fasting status and mutually adjusted for glucose, triglycerides, total cholesterol

Supplementary material

Table S1: Comparison of characteristics between included and excluded participants, Swedish AMORIS cohort

Characteristics	Included (N= 14,150)	Excluded (N=8986)
Age at diagnosis (years)		
Mean (SD)	68 (8.0)	69 (8.3)
CCI		
N (%)		
0	10776 (76.2)	6609 (73.5)
1	1755 (12.4)	1199 (13.3)
2	1056 (7.5)	675 (7.5)
3+	453 (3.2)	434 (4.8)
Missing	110 (0.8)	69 (0.8)
Education		
N (%)		
High	4396 (31.1)	2427 (27.0)
Intermediate	5843 (41.3)	3538 (39.3)
Low	3698 (26.1)	2553 (28.4)
Missing	213 (1.5)	468 (5.2)
Glucose (mmol/L)		
Mean (SD)	5.2 (1.2)	5.2 (1.3)
Triglycerides (mmol/L)		
Mean (SD)	1.6 (1.2)	1.5 (1.0)
Total cholesterol (mmol/L)		
Mean (SD)	5.9 (1.0)	5.9 (1.1)
Vital status		
Alive	10927 (77.2)	5683 (63.2)
All deaths	3223 (22.8)	3303 (36.7)
Prostate cancer deaths	1473 (10.4)	1275 (14.2)
CVD deaths	722 (5.1)	735 (8.2)
Other deaths	1028 (7.3)	1293 (14.4)

- **Abbreviations**: N= number

Table S2: Adjusted hazard ratios (HRs) and 95% CI for the association between overall, and cause-specific death among Swedish men with fasting glucose, triglycerides and total cholesterol measurements.

	Overall death		Prostate cancer death		CVD death		Other death	
	No. of deaths	**HR (95% CI)**	**No. of deaths**	**HR (95% CI)**	**No. of deaths**	**HR (95% CI)**	**No. of deaths**	**HR (95% CI)**
Glucose (mmol/L)								
<5.60	**1422**	1.00 (Ref)	**682**	1.00 (Ref)	**318**	1.00 (Ref)	**422**	1.00 (Ref)
5.6-6.9	**382**	1.16 (1.03-1.31)	**162**	1.10 (0.92-1.32)	**79**	0.88 (0.67-1.16)	**121**	1.48 (1.21-1.80)
>6.9	**108**	1.53 (1.23-1.90)	**44**	1.56 (1.12-2.16)	**27**	1.56 (1.01-2.40)	**37**	1.52 (1.03-2.25)
P for trend		**<0.01**		**0.01**		**0.44**		**<0.01**
Quartiles (mmol/L)								
≤4.5	**334**	1.00 (Ref)	**162**	1.00 (Ref)	**78**	1.00 (Ref)	**94**	1.00 (Ref)
4.6-4.8	**484**	1.02 (0.88-1.19)	**231**	1.06 (0.86-1.30)	**104**	0.95 (0.70-1.30)	**149**	1.02 (0.78-1.33)
4.9-5.4	**528**	0.99 (0.87-1.12)	**253**	1.03 (0.85-1.25)	**116**	0.93 (0.71-1.23)	**159**	0.96 (0.76-1.22)
≥5.5	**566**	1.19 (1.04-1.36)	**242**	1.17 (0.96-1.42)	**126**	0.98 (0.74-1.30)	**198**	1.40 (1.11-1.77)
P for trend		**0.02**		**0.16**		**0.87**		**<0.01**
Triglycerides (mmol/L)								
<1.70	**1321**	1.00 (Ref)	**628**	1.00 (Ref)	**283**	1.00 (Ref)	**410**	1.00 (Ref)
1.70-2.24	**302**	1.01 (0.88-1.15)	**122**	0.99 (0.82-1.20)	**68**	1.17 (0.89-1.53)	**102**	0.93 (0.73-1.19)
≥2.25	**289**	1.17 (1.03-1.34)	**128**	1.08 (0.89-1.32)	**73**	1.32 (1.01-1.75)	**88**	1.20 (0.95-1.53)
P for trend		**0.04**		**0.50**		**0.04**		**0.25**
Quartiles (mmol/L)								
≤0.8	**423**	1.00 (Ref)	**219**	1.00 (Ref)	**89**	1.00 (Ref)	**115**	1.00 (Ref)
0.9-1.2	**529**	1.22 (1.07-1.40)	**242**	1.13 (0.93-1.37)	**107**	1.19 (0.88-1.62)	**180**	1.44 (1.14-1.82)
1.3-1.8	**501**	1.24 (1.09-1.41)	**220**	1.19 (0.99-1.43)	**118**	1.50 (1.13-1.97)	**163**	1.19 (0.94-1.50)
≥1.90	**459**	1.30 (1.14-1.50)	**207**	1.19 (0.98-1.47)	**110**	1.51 (1.12-2.04)	**142**	1.38 (1.07-1.76)
P for trend		**<0.01**		**0.06**		**<0.01**		**0.06**
Total cholesterol (mmol/L)								
<5.18	**408**	1.00 (Ref)	**195**	1.00 (Ref)	**69**	1.00 (Ref)	**144**	1.00 (Ref)
5.18-6.19	**717**	0.92 (0.82-1.04)	**332**	0.88 (0.74-1.05)	**160**	1.29 (0.97-1.72)	**225**	0.86 (0.66-1.01)
>6.19	**787**	0.93 (0.82-1.05)	**361**	0.89 (0.75-1.07)	**195**	1.31 (1.01-1.77)	**231**	0.79 (0.64-0.98)
P for trend		**0.29**		**0.28**		**0.07**		**0.04**
Quartiles (mmol/L)								
≤5.1	**408**	1.00 (Ref)	**195**	1.00 (Ref)	**69**	1.00 (Ref)	**144**	1.00 (Ref)
5.2-5.8	**500**	0.89 (0.73-1.08)	**231**	0.89 (0.73-1.08)	**116**	1.42 (1.05-1.93)	**153**	0.75 (0.59-0.95)
5.9-6.5	**500**	0.92 (0.76-1.11)	**242**	0.92 (0.76-1.11)	**112**	1.16 (0.85-1.58)	**146**	0.86 (0.69-1.09)
≥6.6	**504**	0.86 (0.71-1.03)	**220**	0.86 (0.71-1.03)	**127**	1.37 (1.03-1.84)	**157**	0.79 (0.63-0.99)
P for trend		**0.25**		**0.16**		**0.13**		**0.12**

- **Abbreviations:** Prostate cancer= prostate cancer, CVD= cardiovascular disease
- Models were adjusted for age, educational level, CCI and mutually adjusted for glucose, triglycerides, and total cholesterol